ORIGINAL ARTICLE

Immunogenicity and Safety of a Meningococcal A Conjugate Vaccine in Africans

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ABSTRACT

BACKGROUND

Group A meningococci are the source of major epidemics of meningitis in Africa. An affordable, highly immunogenic meningococcal A conjugate vaccine is needed.

METHODS

We conducted two studies in Africa to evaluate a new MenA conjugate vaccine (PsA-TT). In study A, 601 children, 12 to 23 months of age, were randomly assigned to receive PsA-TT, a quadrivalent polysaccharide reference vaccine (PsACWY), or a control vaccine (*Haemophilus influenzae* type b conjugate vaccine [Hib-TT]). Ten months later, these children underwent another round of randomization within each group to receive a full dose of PsA-TT, a one-fifth dose of PsACWY, or a full dose of Hib-TT, with 589 of the original participants receiving a booster dose. In study B, 900 subjects between 2 and 29 years of age were randomly assigned to receive PsA-TT or PsACWY. Safety and reactogenicity were evaluated, and immunogenicity was assessed by measuring the activity of group A serum bactericidal antibody (SBA) with rabbit complement and performing an IgG group A–specific enzyme-linked immunosorbent assay.

RESULTS

In study A, 96.0% of the subjects in the PsA-TT group and 63.7% of those in the PsACWY group had SBA titers that were at least four times as high as those at baseline; in study B, 78.2% of the subjects in the PsA-TT group and 46.2% of those in the PsACWY group had SBA titers that were at least four times as high as those at baseline. The geometric mean SBA titers in the PsA-TT groups in studies A and B were greater by factors of 16 and 3, respectively, than they were in the PsACWY groups ($P<0.001$). In study A, the PsA-TT group had higher antibody titers at week 40 than the PsACWY group and had obvious immunologic memory after receiving a polysaccharide booster vaccine. Safety profiles were similar across vaccine groups, although PsA-TT recipients were more likely than PsACWY recipients to have tenderness and induration at the vaccination site. Adverse events were consistent with age-specific morbidity in the study areas; no serious vaccine-related adverse events were reported.

CONCLUSIONS

The PsA-TT vaccine elicited a stronger response to group A antibody than the PsACWY vaccine. (Funded by the Meningitis Vaccine Project through a grant from the Bill and Melinda Gates Foundation; Controlled-Trials.com numbers, ISRCTN78147026 and ISRCTN87739946.)

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For more than a century, major meningococcal meningitis epidemics have occurred every 10 to 12 years in what is known as the African meningitis belt, which stretches from Senegal to Ethiopia.[1-3] The majority of these epidemics have been caused by group A *Neisseria meningitidis*, and incidence rates have been as high as 500 cases per 100,000 population, with most cases occurring in persons between 1 and 29 years of age.[4,5] In 2009, more than 50,000 cases of group A meningococcal meningitis were reported in northern Nigeria.[6] Because of the epidemic potential and high disease burden of group A meningococcal disease, controlling it is a public health priority in Africa.[1-3,7]

To address this problem, the World Health Organization (WHO) has emphasized case management and reactive emergency vaccination with polysaccharide vaccines.[8,9] Although group A polysaccharide vaccine induces a solid antibody response in persons between 1 and 29 years of age and has been shown to be effective in African field trials,[10-12] reactive vaccination campaigns are expensive and logistically difficult, and they have not eliminated meningococcal epidemics. In addition, the immunity induced by polysaccharide vaccines is short-lived and has little or no effect on carriage.[13,14]

In response to the need for more effective meningococcal vaccines in Africa, the Meningitis Vaccine Project (MVP), a partnership between the WHO and the Program for Appropriate Technology in Health (PATH), an international nonprofit organization, was established in 2001 with funding from the Bill and Melinda Gates Foundation. The goal of this partnership is to eliminate epidemics of group A meningitis through the development, testing, licensure, and introduction of a group A meningococcal conjugate vaccine that would be affordable in Africa.[15] The new group A meningococcal conjugate vaccine, referred to here as PsA-TT, costs less than 50 cents per dose.[15,16] After the completion of a phase 1 study involving healthy adults in India,[17] two clinical studies were conducted to evaluate the safety and immunogenicity of a single dose of the PsA-TT vaccine as compared with that of a licensed vaccine with activity against meningococcal polysaccharide groups A, C, Y, and W135 in persons between 1 and 29 years of age. We report the results of both studies.

Methods

Study Design and Oversight

Studies A and B were double-blind, randomized, controlled, comparative trials designed to evaluate the immunogenicity and safety of a single injection of PsA-TT vaccine in healthy residents of the study areas; study A was also designed to evaluate the ability of the vaccine to induce immunologic memory. Study A was conducted among healthy children between 12 and 23 months of age at Centre pour le Développement des Vaccins in Bamako, Mali, and the Medical Research Council Laboratories in Basse, Gambia. Study B was conducted among healthy children and adults between 2 and 29 years of age in Mali, in Gambia, and at the Institut de Recherche pour le Développement in Niakhar, Senegal.

The participants in study A were 601 children, 12 to 23 months of age, who were randomly assigned in equal proportions to receive PsA-TT (MenAfriVac, Serum Institute of India); a reference vaccine, PsACWY (Mencevax ACWY, GlaxoSmithKline); or a control vaccine, *Haemophilus influenzae* type b conjugate Hib-TT, (Hiberix, GlaxoSmithKline). Ten months later, 589 of the participants underwent within-group randomization to receive a booster vaccination with a full dose of PsA-TT, one-fifth of a full dose of PsACWY, or a full dose of Hib-TT.[18] In study B, participants between 2 and 29 years of age were recruited and evenly stratified according to age into three groups: 2 to 10 years, 11 to 17 years, and 18 to 29 years. They were then randomly assigned in a ratio of 2:1 to receive the PsA-TT vaccine or the PsACWY vaccine. Immunogenicity, reactogenicity, and short-term safety were assessed 4 weeks after both the primary and booster vaccinations were administered in study A and 4 weeks after the primary vaccination in study B. Immunogenicity was also evaluated 10 months after primary vaccination and 1 week after booster vaccination in study A. Only the staff members at the study sites who were responsible for preparing the vaccines were aware of group assignments; the subjects, other site staff members, investigators, laboratory personnel, and sponsors were unaware of group assignments throughout the study period.

The main criteria for exclusion were a history of vaccination against *N. meningitidis* within the preceding 6 years, known exposure to *N. meningitidis*

within the preceding 3 months, allergy or known hypersensitivity after any vaccination, and a positive pregnancy test. (Further details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Both studies were conducted in accordance with the study protocols (available at NEJM.org).

The trials were designed and conducted in accordance with the Good Clinical Practice Guidelines established by the International Conference on Harmonization and with the Declaration of Helsinki.

The Serum Institute of India provided all vaccines except the Mencevax vaccine used in study A, which was provided by GlaxoSmithKline; all vaccines were provided free of charge. All authors contributed to the writing of the study and participated in the decision to publish the manuscript. Each participating community provided permission to conduct the study, and written informed consent was obtained before enrollment from all subjects between 18 and 29 years of age and from all parents or guardians of subjects younger than 18 years of age. Information on approval of the study by various committees charged with monitoring research involving human subjects is provided in the Supplementary Appendix.

VACCINES

A reconstituted dose of PsA-TT vaccine (0.5 ml) contained 10 μg of group A polysaccharide conjugated to 10 to 33 μg of tetanus toxoid, 0.3 mg Al^{3+} in $AlPO_4$ (aluminum phosphate) as adjuvant, TRIS buffer, 0.01% thimerosal, and 0.9% sodium chloride. A reconstituted dose of reference vaccine, PsACWY (0.5 ml), contained 50 μg of purified polysaccharide from each of the *N. meningitidis* groups A, C, Y, and W135; lactose; sodium chloride; and water for injection. A reconstituted dose of the control vaccine, Hib-TT (0.5 ml), used in study A contained 10 μg of the polyribosylribitol phosphate capsular polysaccharide of *H. influenzae* type b (Hib) conjugated to 20 to 40 μg of tetanus toxoid, lactose, and sodium chloride. Vaccines were injected intramuscularly in the right deltoid unless participants were younger than 2 years of age, in which case, the right thigh was injected; the one-fifth booster doses of the PsACWY vaccine were administered subcutaneously in the right deltoid.[19]

IMMUNOLOGIC EVALUATION

Blood samples were obtained before vaccination and 4 weeks after the primary vaccination in study A and the single vaccination in study B. In study A, samples were also obtained before the booster vaccination (i.e., 10 months after primary vaccination), 1 week and 4 weeks after the booster vaccination. For each blood sample collected, a thick smear was examined for malaria. The immunogenicity of the PsA-TT vaccine and the group A component of the PsACWY vaccine was assessed by measuring the activity of group A serum bactericidal antibody (SBA) with rabbit complement and performing a group A–specific IgG enzyme-linked immunosorbent assay (ELISA). Measurement of SBA titers was performed at the Health Protection Agency, Manchester, United Kingdom,[20] and the ELISA was performed at the Centers for Disease Control and Prevention (CDC), Atlanta, with the use of the standard reference serum CDC1992.[21] The SBA reference strain was F8238, and titers were expressed as the reciprocal of the final serum dilution, resulting in a colony-count reduction of at least 50% after 60 minutes of incubation.

The primary end point for immunogenicity was seroconversion, defined as an SBA titer that was at least four times as high as that at baseline 28 days after immunization (e.g., baseline titers ≤4 required postimmunization titers ≥16). Other end points included a level of group A–specific IgG that was at least 4 times as high as that at baseline, an SBA titer of 8 or more and 128 or more,[22] percentages of subjects with a group A–specific IgG concentration of 2 μg per milliliter or more, geometric mean titer, and geometric mean concentration.

SAFETY EVALUATION

Subjects were observed for 30 minutes after vaccination to record and treat immediate reactions. Subjects were monitored for local and systemic postimmunization reactions during daily home visits for 4 days; adverse events were assessed for 1 month, and serious adverse events were assessed throughout the course of each study. Subjects (or their parents or guardians) were asked about tenderness and induration at the vaccination site; fever, vomiting, and diarrhea (for all subjects) as well as lethargy, irritability, and loss of appetite (for subjects between 1 and 10 years of age) and

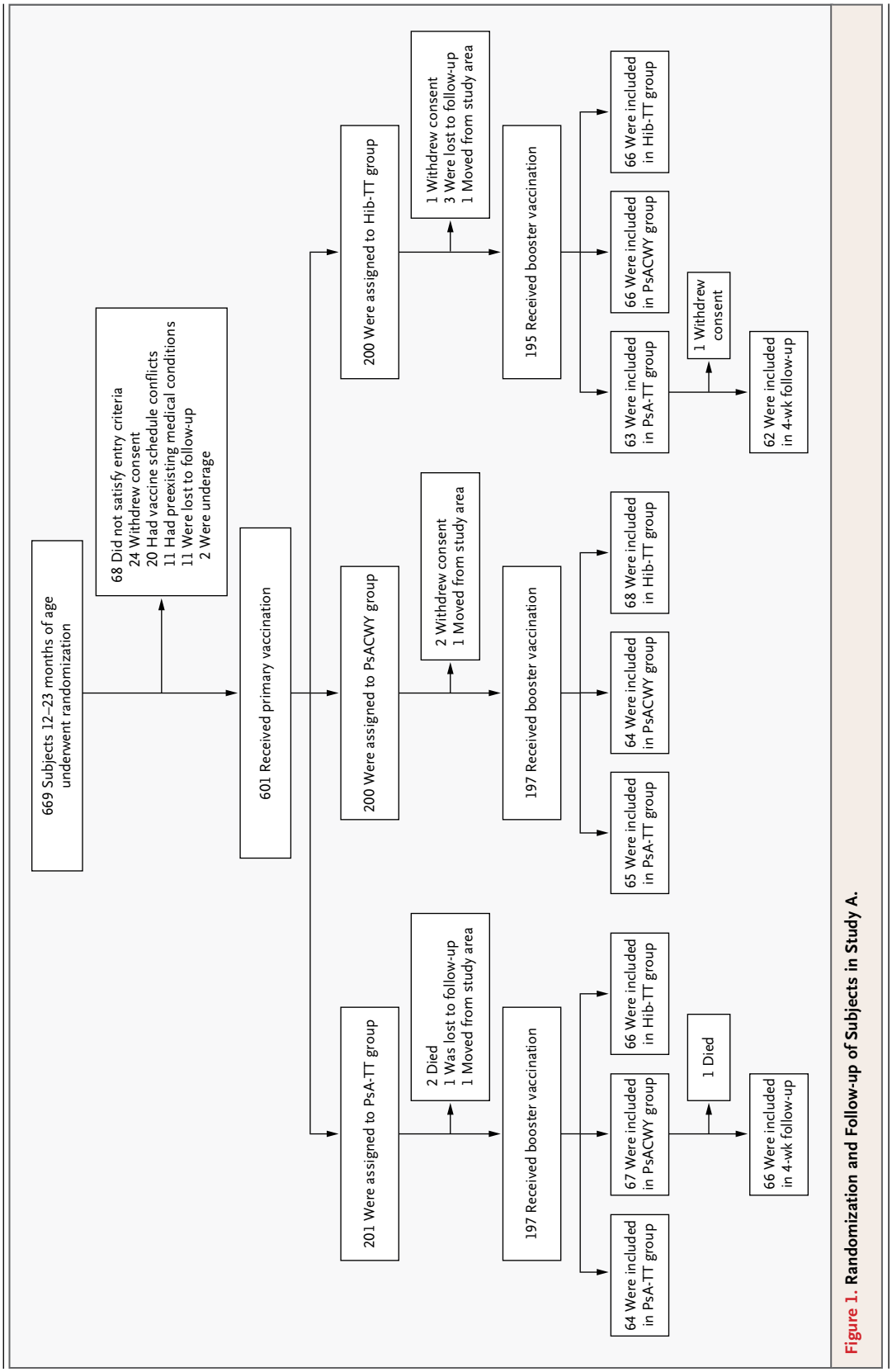

Figure 1. Randomization and Follow-up of Subjects in Study A.

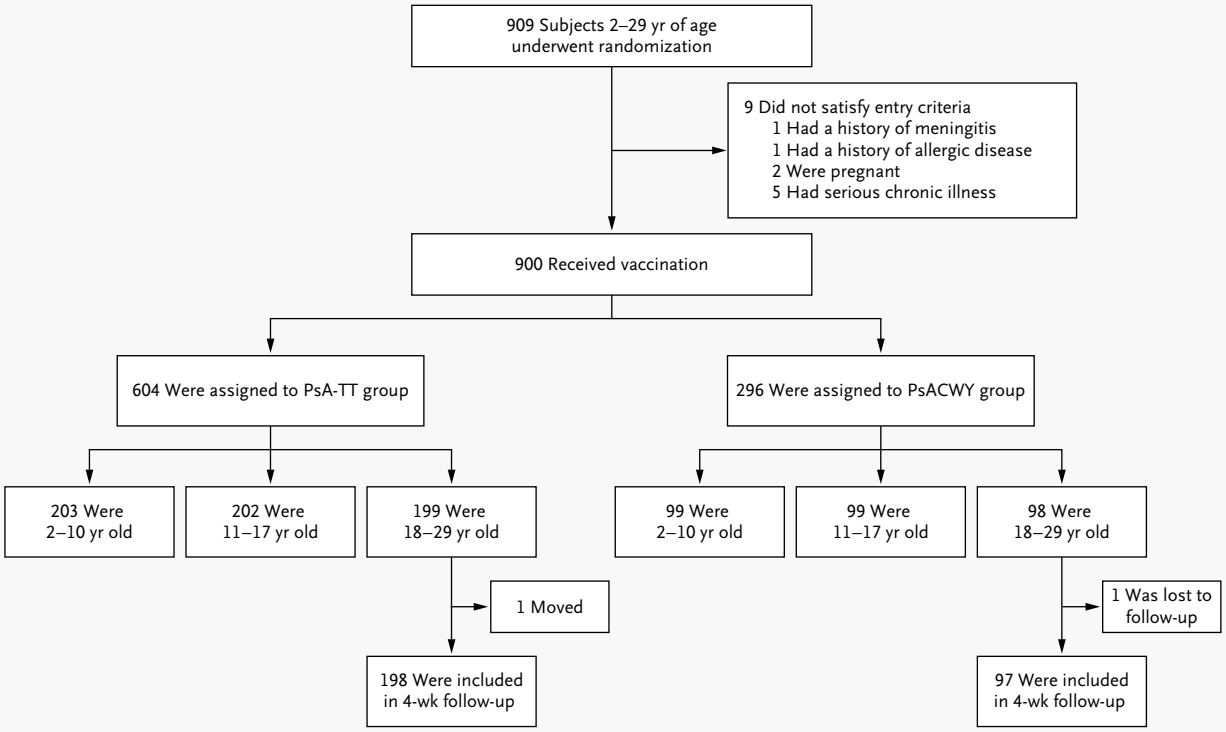

Figure 2. Randomization and Follow-up of Subjects in Study B.

headache, fatigue, myalgia, and arthralgia (for subjects older than 10 years of age). Solicited reactions within 4 days were presumed to be vaccine-related. Assessment of causality in the case of unsolicited adverse events was performed by the study investigators at each site. A data and safety monitoring board was established for studies A and B.

STATISTICAL ANALYSIS

The primary objective of each study was to demonstrate that the PsA-TT vaccine was not inferior to the PsACYW vaccine, as determined by the achievement of an SBA titer that was at least four times as high as that at baseline (noninferiority margin for the titer increase, 0.10). The 95% confidence interval for the difference in the proportions of subjects with this response in the PsACWY and PsA-TT groups was calculated with the use of the Miettinen–Nurminen method.[23] If the upper limit of the confidence interval was less than 0.10, the PsA-TT vaccine was considered to be noninferior to the PsACWY vaccine. The exact 95% confidence intervals for the binomial proportions were calculated for all applicable secondary end points in each vaccine group. The Cochran–Mantel–Haenszel test was used to compare the proportions between vaccine groups with adjustment for age in study B. Student's t-test and Fisher's exact test were used to compare the groups as appropriate. Reverse cumulative distribution curves were generated 4 weeks after primary immunization. All immunogenicity and safety analyses were conducted in the intention-to-treat population. Missing values were treated as missing at random. Data were analyzed with SAS software, version 9.1.3. Calculations of the sample size required for the noninferiority assessment were based on formulas derived by Farrington and Manning[24] (see the Supplementary Appendix for details).

RESULTS

STUDY POPULATION

In study A, among the 669 subjects who underwent randomization, 601 (300 in Mali and 301 in the Gambia) received the primary vaccination between September 18 and November 6, 2006; and 589 received a booster vaccination 10 months later (Fig. 1). In study B, among the 909 subjects who underwent randomization, 900 were vacci-

Table 1. Immunogenicity Results in the Two Studies.*

Vaccine	Week 0, Preprimary	Week 4, Postprimary	Week 40, Prebooster	Week 41, 7 Days after Booster	Week 44, 28 Days after Booster
Study A — 12–23 mo of age					
			Serum Bactericidal Antibody GMT (95% CI)		
Primary					
PsA-TT	14.3 (9.9–20.7)	6234.5 (4947.9–7855.7)†	1167.9 (873.7–1561.3)†		
Booster					
PsA-TT			1130.6 (666.0–1919.2)	21,720.7 (17,706.0–26,645.6)‡	10,037.4 (7884.5–12,778.2)‡
PsACWY			1735.6 (1136.3–2650.8)	8679.1 (7135.4–10,556.8)‡	5048.3 (4144.0–6149.9)‡
Hib-TT			801.3 (457.6–1403.1)	1448.2 (918.3–2283.7)‡	1649.1 (1022.7–2659.3)‡
Primary					
PsACWY	16.2 (10.9–24.1)	365.3 (248.7–536.5)†	47.2 (31.1–71.6)†		
Booster					
PsA-TT			42.9 (20.8–88.3)	12,214.2 (9435.7–15,810.8)	6708.9 (5097.6–8829.5)
PsACWY			61.3 (28.2–133.0)	2294.5 (1799.6–2925.4)‡	692.4 (379.9–1261.9)‡
Hib-TT			40.5 (20.1–81.5)	103.4 (51.1–209.1)‡	190.8 (91.1–399.4)‡
Primary					
Hib-TT	12.6 (8.7–18.2)	60.9 (39.8–93.2)	52.6 (34.1–81.0)		
Booster					
PsA-TT			42.6 (20.3–89.4)	14,063.4 (10,939.9–18,078.9)‡	9342.9 (7043.8–12,392.4)‡
PsACWY			66.0 (30.8–141.5)	4418.6 (3281.0–5950.7)‡	1562.2 (957.7–2548.4)‡
Hib-TT			51.2 (23.5–111.5)	76.3 (35.2–165.4)	268.1 (128.0–561.5)
			Group A–Specific IgG GMC (95% CI) *μg/ml*		
Primary					
PsA-TT	0.1 (0.1–0.1)	18.2 (16.0–20.7)†	1.0 (0.9–1.3)†		
Booster					
PsA-TT			1.0 (0.8–1.4)	69.2 (49.6–96.5)‡	38.1 (25.5–57.2)‡
PsACWY			1.1 (0.8–1.5)	18.3 (13.9–24.2)‡	15.0 (11.6–19.3)‡
Hib-TT			1.0 (0.7–1.4)	1.1 (0.8–1.5)‡	1.1 (0.7–1.6)‡
Primary					
PsACWY	0.1 (0.1–0.1)	1.5 (1.2–1.9)†	0.4 (0.4–0.5)†		
Booster					
PsA-TT			0.4 (0.3–0.5)	34.0 (24.9–46.3)	38.1 (29.7–48.9)
PsACWY			0.5 (0.3–0.7)	3.3 (2.1–5.1)‡	3.2 (2.0–5.1)‡
Hib-TT			0.5 (0.3–0.6)	0.5 (0.4–0.7)‡	0.5 (0.3–0.6)‡

Primary					
Hib-TT	0.1 (0.1–0.2)	0.1 (0.1–0.1)	0.1 (0.1–0.2)		
Booster					
PsA-TT			0.1 (0.1–0.2)	15.8 (10.7–23.2)‡	15.4 (11.7–20.2)‡
PsACWY			0.1 (0.1–0.2)	1.9 (1.3–2.8)‡	1.8 (1.2–2.6)‡
Hib-TT			0.2 (0.1–0.2)	0.2 (0.1–0.2)	0.2 (0.1–0.2)
Study B — 2–29 yr of age§					
			Serum Bactericidal Antibody GMTs (95% CI)		
Primary					
PsA-TT	223.3 (181.3–274.9)	4712.6 (4336.0–5122.0)†			
PsACWY	316.0 (240.4–415.3)	1191.4 (969.1–1464.6)†			
			Group A–Specific IgG GMC (95% CI) *μg/ml*		
Primary					
PsA-TT	2.1 (1.9–2.5)	65.6 (60.0–71.6)†			
PsACWY	1.9 (1.5–2.3)	12.9 (10.9–15.3)†			

* Values for serum bactericidal antibody with rabbit complement are geometric mean titers (GMTs); IgG values are geometric mean concentrations (GMCs).
† For serum bactericidal antibody titers and IgG levels, P<0.001 by Student's t-test for the comparison of PsA-TT with PsACWY at week 4 in both studies and at week 40 in study A.
‡ For serum bactericidal antibody titers and IgG levels in study A, P<0.001 by Student's t-test for the following comparisons: PsACWY/PsACWY versus PsA-TT/PsA-TT, PsACWY/Hib-TT versus PsA-TT/Hib-TT, PsACWY/PsACWY versus PsA-TT/PsACWY, and Hib-TT/PsACWY versus Hib/PsA-TT at week 41 and week 44, except that P=0.002 for IgG levels at week 41 for PsACWY/Hib-TT versus PsA-TT/Hib-TT. (Slash marks separate the primary and booster vaccines.)
§ The results for the age groups from 2 to 10 years of age, 11 to 17 years of age, and 18 to 29 years of age are available in the Supplementary Appendix.

nated (300 subjects each in Mali, the Gambia, and Senegal) (Fig. 2). All vaccinated subjects were included in the analyses. Immunogenicity data on SBA titers were available for at least 93% of the subjects at each time point in both studies. Demographic and clinical characteristics of the subjects are summarized in the Supplementary Appendix.

IMMUNOGENICITY

Immunogenicity was measured 4 weeks after primary vaccination. In study A, 96.0% of the subjects in the PsA-TT group (95% confidence interval [CI], 92.2 to 98.2) had SBA titers that were at least four times as high as those at baseline, as compared with 63.7% of subjects in the PsACWY group (95% CI, 56.5 to 70.5) and 35.6% of those in the Hib-TT group (95% CI, 28.8 to 42.7). In study B, 78.2% of the subjects in the PsA-TT group (95% CI, 74.7 to 81.5) and 46.2% of those in the PsACWY group (95% CI, 40.4 to 52.1) had titers that were at least four times as high as those at baseline. Similar changes in titer were noted across all age groups. On the basis of guidelines from the European Medicines Agency, the differences between the PsACWY and PsA-TT groups of –32.2 percentage points (95% CI, –39.6 to –25.0%) in study A and –32.0 percentage points (95% CI, –38.5% to –25.4%) in study B support a claim of superiority for the PsA-TT vaccine (P<0.001 for both comparisons).[25]

In studies A and B, the geometric mean SBA titers (Table 1) and the proportions of subjects with SBA titers of 128 or more after vaccination were significantly higher in the PsA-TT group than in the other vaccine groups (for details, see the Supplementary Appendix). Postimmunization levels of group A–specific IgG were significantly higher in the PsA-TT vaccine group than in the other vaccine groups in both studies and across all age groups. (See Table 1 for geometric mean concentrations according to vaccine type, and see the Supplementary Appendix for titers that were at least four times as high as those at baseline and for percentages of subjects with an IgG level of 2 μg per milliliter or more.) Reverse cumulative distribution curves for SBA titers according to study and age group are shown in Figure 3; postimmunization results were consistently better with the PsA-TT vaccine.

PERSISTENCE OF IMMUNOLOGIC RESPONSE

Forty weeks after the primary vaccination in study A, the proportions of subjects who still had an

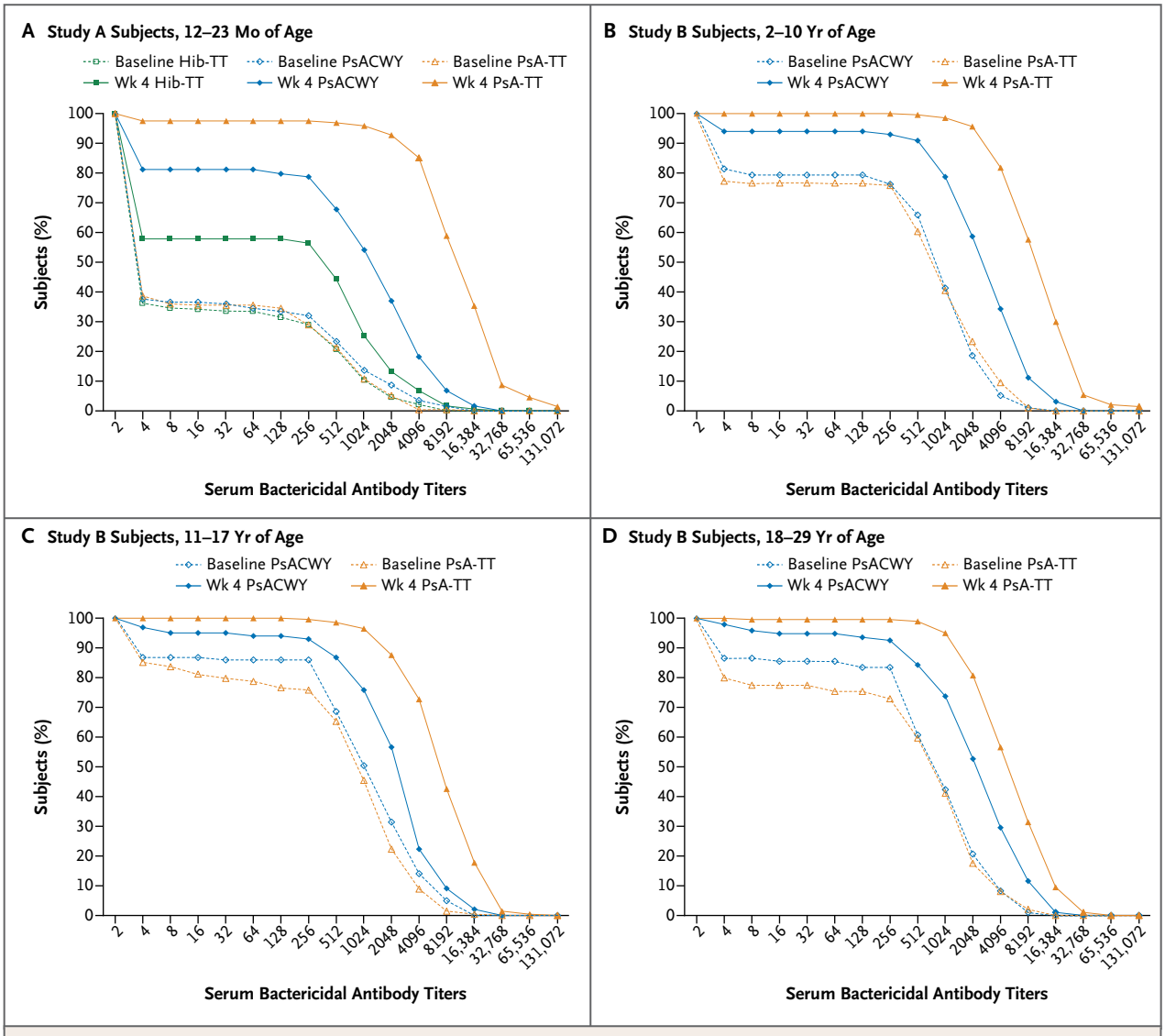

Figure 3. Reverse Cumulative Distribution Curves for Antibody Titers in Studies A and B, According to the Vaccine Group and the Age of the Subjects.

Subjects in study A were randomly assigned to the MenA conjugate vaccine (PsA-TT), a quadrivalent polysaccharide reference vaccine (PsACWY), or a control vaccine (*Haemophilus influenzae* type b conjugate vaccine [Hib-TT]); subjects in study B were randomly assigned to PsA-TT or PsACWY. Serum bactericidal antibody activity with rabbit complement was measured at baseline and 4 weeks after primary vaccination. Results are shown for subjects in study A, who were 12 to 23 months old (Panel A), and subjects in Study B, who were assigned by age to one of three groups: those 2 to 10 years old (Panel B), those 11 to 17 years old (Panel C), and those 18 to 29 years old (Panel D). All x-axis values are titers expressed as reciprocals of serum dilutions.

increase by a factor of 4 or more in the SBA titer, as compared with the preimmunization titer, were 82.1% (95% CI, 75.9 to 87.2) in the PsA-TT group, 38.3% (95% CI, 31.4 to 45.5) in the PsACWY group, and 38.3% (95% CI, 31.5 to 45.6) in the Hib-TT group. The geometric mean SBA titers in the three groups were 1167.9 (95% CI, 873.7 to 1561.3), 47.2 (95% CI, 31.1 to 1.6), and 52.6 (95% CI, 34.1 to 81.0), respectively, and the proportions of subjects with SBA titers of 128 or more were 92.3% (95% CI, 87.6 to 95.6), 54.6% (95% CI, 47.3 to 61.7), and 54.1% (95% CI, 46.8 to 61.3), respectively.

A similar pattern characterized the between-group differences in geometric mean concentrations of group A–specific IgG, which were as follows: 1.0 μg per milliliter (95% CI, 0.9 to 1.3) in the PsA-TT group, 0.4 μg per milliliter (95% CI, 0.4 to 0.5) in the PsACWY group, and 0.1 μg per milliliter (95% CI, 0.1 to 0.2) in the Hib-TT group. Significant differences were also found between the PsA-TT vaccine group and the PsACWY and Hib-TT groups for the other end points based on group A–specific IgG values (a level that was at least four times as high as that at baseline and percentages of subjects with a concentration of 2 μg or more per milliliter); these data are provided in the Supplementary Appendix.

IMMUNOLOGIC MEMORY

To evaluate the ability of the study vaccines to induce immunologic memory, we measured geometric mean SBA titers and geometric mean concentrations of group A–specific IgG 7 days after the booster vaccination in study A. Among the subjects who received one fifth of the full dose of the PsACWY vaccine, geometric mean SBA titers were 8679.1 in the group primed with the PsA-TT, 2294.5 in the group primed with PsACWY, and 4418.6 in the group primed with Hib-TT. Among subjects who received PsA-TT as the booster dose, the geometric mean SBA titers were 21720.7 in the group primed with PsA-TT, 12214.2 in the group primed with PsACWY, and 14063.4 in the group primed with Hib-TT (Table 1). Serologic data recorded 28 days after the administration of boosters, summarized in Table 1, showed similar trends.

SAFETY

Postimmunization reactions and adverse events are shown in Table 2. No reactions occurred immediately after immunization. Rates of injection-site and systemic reactions during the first 4 days after immunization and rates of adverse events during the first 28 days after immunization were similar among vaccine groups. However, induration in study A and tenderness in study B were reported more frequently after primary vaccination in the PsA-TT group, whereas vomiting in study A and fatigue in study B were reported more frequently in the PsACWY group. Diarrhea (in study A), headache (in study B, among subjects 11 to 29 years of age), and fever (in study B, among subjects in all age groups — 2 to 29 years of age) were the most frequently reported systemic postimmunization reactions after primary vaccination. Local and systemic postimmunization reactions were transient and mild and resolved without sequelae.

Commonly reported adverse events included malaria, respiratory infections, gastroenteritis, and conjunctivitis. All adverse events resolved without sequelae, and no vaccine-related adverse events were recorded. In study A, 16 serious adverse events were reported within 2 years after primary vaccination, and in study B, 5 serious adverse events in 5 subjects were recorded within 1 year. In study A, 5 of the 16 serious adverse events were fatal; no deaths were reported in study B. In both studies there were no significant differences among vaccine groups with respect to serious adverse events after vaccination (Table 2). For detailed data on solicited local and systemic reactions, adverse events, and serious adverse events, see the Supplementary Appendix.

DISCUSSION

The level of SBA activity correlates with the degree of protection against meningococcal disease.[26,27] An SBA titer at least four times as high as that at baseline is accepted as a criterion for seroconversion and has been used to support the licensing of the meningococcal conjugate vaccines Menactra (Sanofi Pasteur) and Menveo (Novartis) in the United States.[28,29] This criterion can be particularly difficult to meet in a population with high baseline titers of antibodies against *N. meningitidis*. Among the subjects in study B who were older than 2 years of age, 75% had baseline functional antibody titers of 128 or higher. Nonetheless, we found that the criterion of an SBA titer at least four times as high as that at baseline worked well across all age groups in comparing the immunogenicity of the PsA-TT conjugate vaccine with that of the reference polysaccharide vaccine, PsACWY. The higher proportion of responses in the PsA-TT group than in the polysaccharide group indicated that the conjugate vaccine was superior.[25]

The maintenance of antibody levels over time is a key determinant of immunologic protection; when antibody levels decline, protection wanes, even if vaccinees are primed for the development of immunologic memory.[30] The proportion of subjects with persistent antibody responses at 40 weeks was significantly higher with PsA-TT

Table 2. Reactions and Adverse Events in the Two Studies.

Immunization and Vaccine Group	Total No. of Subjects	Local Reactions, ≤4 Days after Immunization		Systemic Reactions, ≤4 Days after Immunization		Adverse Events, ≤28 Days after Immunization		Serious Adverse Events, ≤280 Days after Immunization or 450 Days after Booster*	
		no.	% (95% CI)	no.	% (95% CI)	no.	% (95% CI)	no.	% (95% CI)
Study A, 12–23 mo of age									
Primary									
PsA-TT	201	27	13.4 (9.0–18.9)†	33	16.4 (11.6–22.3)	69	34.3 (27.8–41.3)	3‡	1.5 (0.3–4.3)
PsACWY	200	10	5.0 (2.4–9.0)†	31	15.5 (10.8–21.3)	62	31.0 (24.7–37.9)	5	2.5 (0.8–5.7)
Hib-TT	200	19	9.5 (5.8–14.4)	31	15.5 (10.8–21.3)	53	26.5 (20.5–33.2)	1	0.5 (0.0–2.8)
Booster									
PsA-TT/PsA-TT	64	2	3.1 (0.4–10.8)	8	12.5 (5.6–23.2)	3	4.7 (1.0–13.1)	0	0 (0.0–5.6)
PsA-TT/PsACWY	67	0	0 (0.0–5.4)	8	11.9 (5.3–22.2)	5	7.5 (2.5–16.6)	1§	1.5 (0.0–8.0)
PsA-TT/Hib-TT	66	0	0 (0.0–5.4)	4	6.1 (1.7–14.8)	4	6.1 (1.7–14.8)	0	0 (0.0–5.4)
PsACWY/PsA-TT	65	1	1.5 (0.0–8.3)	6	9.2 (3.5–19.0)	7	10.8 (4.4–20.9)	2§	3.1 (0.4–10.7)
PsACWY/PsACWY	64	0	0 (0.0–5.6)	11	17.2 (8.9–28.7)	6	9.4 (3.5–19.3)	1¶	1.6 (0.0–8.4)
PsACWY/Hib-TT	68	1	1.5 (0.0–7.9)	4	5.9 (1.6–14.4)	7	10.3 (4.2–20.1)	1	1.5 (0.0–7.9)
Hib-TT/PsA-TT	63	1	1.6 (0.0–8.5)	12	19.0 (10.2–30.9)	5	7.9 (2.6–17.6)	0	0 (0.0–5.7)
Hib-TT/PsACWY	66	0	0 (0.0–5.4)	5	7.6 (2.5–16.8)	12	18.2 (9.8–29.6)	0	0 (0.0–5.4)
Hib-TT /Hib-TT	66	1	1.5 (0.0–8.2)	9	13.6 (6.4–24.3)	6	9.1 (3.4–18.7)	1	1.5 (0.0–8.2)
Study B, 2–29 yr of age‖									
Primary									
PsA-TT	604	34	5.6 (3.9–7.8)**	18	3.0 (1.8–4.7)	56	9.3 (7.1–11.9)	2	0.3 (0.0–1.2)
PsACWY	296	5	1.7 (0.6–3.9)**	5	1.7 (0.6–3.9)	28	9.5 (6.4–13.4)	3	1.0 (0.2–2.9)

* For study B, data apply to serious adverse events 392 days after immunization.

† P=0.005 by Fisher's exact test for the comparison of PsACWY with PsA-TT. The difference was mainly due to an excess of indurations reported at one site (Mali).

‡ A total of 10 serious adverse events were reported after primary immunization, 2 of which occurred in one subject in the Hib-TT group: 2 cases of bronchopneumonia 106 and 272 days after immunization. Two cases of serious adverse events resulted in death: protein energy malnutrition and acute gastroenteritis 226 and 250 days after immunization in the PsA-TT group.

§ After the booster immunization, a total of 6 serious adverse events were reported in 6 subjects. Three cases of serious adverse events resulted in death: one from complication of marasmus 42 days after immunization in the PsA-TT/PsACWY group, one from cerebral malaria 356 days after immunization in the PsACWY/PsA-TT group, and one from hemorrhage caused by internal injuries resulting from a car accident 398 days after immunization in the PsACWY/PsA-TT group.

¶ One serious adverse event was a case of meningococcal A meningitis in the PsACWY/PsACWY group, which occurred in Mali at the end of the 2008 dry season in a 2-year-old boy. He was promptly treated and recovered without sequelae. Serologic results subsequently revealed that he had a response to primary vaccination with the PsACWY vaccine, but the immunologic response subsided rapidly to preimmunization antibody levels. The subject had a response to a booster of PsACWY vaccine (one fifth of a dose), but the immunologic response again subsided rapidly to preimmunization antibody levels, with no evidence of an anamnestic response.

‖ The results for the age groups from 2 to 10 years of age, 11 to 17 years of age, and 18 to 29 years of age, are available in the Supplementary Appendix. Systemic reaction reported for Study B includes fever, vomiting and diarrhea. See the Supplementary Appendix for details.

** P=0.01 by the Cochran–Mantel–Haenszel test for the comparison of PsACWY with PsA-TT after adjustment for age group; the difference was due to more reports of tenderness in the PsA-TT group than in the PsACWY group.

than with PsACWY, which suggests that recipients of the PsA-TT vaccine would have the benefit of a longer period of protection.

Conjugate vaccines, by recruiting T-helper cells, induce immunologic memory,[31] whereas T-cell–independent polysaccharide vaccines are characterized by hyporesponsiveness after repeated administration.[32] In study A, 7 and 28 days after a booster vaccination with PsACWY at one fifth of the full dose (10 μg), subjects who had been primed with the PsA-TT vaccine had significantly higher geometric mean SBA titers than those who had been primed with the PsACWY or Hib-TT vaccine. The decline in SBA from day 7 to day 28 may be attributable to the early rapid expansion of antibody-secreting cells, and thus increased antibody production, followed by a contraction or down-regulation of antibody-secreting cells as antigen becomes less available. Similar findings have been reported in other studies.[33,34]

A study conducted in the United States compared the effectiveness of a meningococcal quadrivalent polysaccharide–diphtheria conjugate vaccine with that of a variant of the PsACWY vaccine in children 2 to 10 years of age. Twenty-eight days after immunization, the geometric mean group A SBA titer was greater by a factor of only 0.9 as compared with the PsACWY vaccine (1700 [95% CI, 1512 to 1912], vs. 893 [95% CI, 791 to 1009] with the PsACWY vaccine),[35] whereas in our two studies, titers were greater by factors of 16 (study A) and 3 (study B). Two other meningococcal quadrivalent conjugate vaccines have been shown to be immunogenic in toddlers and young children.[36,37]

Our data show that the new group A meningococcal conjugate vaccine, when tested in Africans between 1 and 29 years of age, had a safety profile similar to that of a licensed polysaccharide vaccine but elicited a significantly stronger and more persistent response from functional antibodies against group A meningococcus. The new vaccine also had the ability to induce immunologic memory. If widespread use of this new vaccine induces herd immunity, as was the case in the United Kingdom with a group C conjugate vaccine, it could potentially decrease epidemics of group A meningococcal infection in the African meningitis belt.

The views expressed in this article are those of the authors and do not necessarily represent the decisions, policies, or views of the WHO.

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